Cholesterol Levels. The importance of cholesterol levels in the blood mentioned in this page and in the next three pages has recently been questioned by Oster (Med Counterpoint 4: 13-27, 1972). The questions raised by the author relate to the value of epidemiologic studies in general. The article is reporduced in its entirety.

Oster K A: Prevention of atherosclerosis.

EDITOR'S NOTE: *Dr. Oster's paper takes issue with certain conclusions of the Inter-Society Commission Report that have been drawn from the Framingham Study concerning the risk of coronary heart disease. It particularly challenges the stated relative effect on risk of CHD at different levels of serum cholesterol. Some of the questioning is based on clinical experience confirmed by others (e.g., the unimportant effect on serum cholesterol levels of significant reductions in dietary cholesterol).*

Moreover, Dr. Oster casts doubt on the value of epidemiologic studies of this type and questions the mathematical underpinnings of the statistical methods employed in this case. To review such matters we have called upon a consulting mathematician to offer a critique of Dr. Oster's remarks as well as the methodology of the Framingham Study. His comments immediately follow Dr. Oster's paper.

In December 1970, The Inter-Society Commission for Heart Disease Resources, "comprised of outstanding leaders in the field of cardiovascular diseases and representatives of national professional organizations capable of making significant contributions," reported its suggestions for the prevention of atherosclerotic diseases.

Dr. Oster is Chief of Cardiology, Park City Hospital, Bridgeport, Conn. The author gratefully acknowledges the assistance of Michael A. Berger in the mathematical analysis of the statistical data in the Report. Mr. Berger, a student at the University of Bridgeport, was supported in this work by a research grant from the Greater Bridgeport Heart Association.

*"Primary Prevention of the Atherosclerotic Diseases": Report of the Inter Society Commission for Heart Disease Resources, Circulation 42 A:55, 1970

The Commission was created through a contract with Regional Medical Programs Service to help fulfill the requirements of Section 907 of Public Law 89-239, which established the Regional Medical Programs in 1965. The Commission worked under contract No. NH 69-29 with the Health, Science, and Mental Health Administration Department of the Department of Health, Education and Welfare. The funds came out of taxpayers' money.

In its introductory note to the reader, the Commission invites constructive criticism of the work of its study groups, particularly those who attempt to apply these guidelines. In the following paper such constructive criticism will be given and it will be shown that the Report of the Commission is prejudicial, based on dubious data and therefore probably deceptive. Furthermore, by thus wasting the taxpayers' money, the Report of the Commission, instead of advancing the cause of coronary heart disease prevention, channels the research funds overwhelmingly into narrow, preconceived, subjective, discredited areas of research. It thereby hinders, if it does not preclude, the development of other approaches which may provide more effective solutions of this problem, so vital to the health of the American people.

To the tune of scheduled press conferences and through recourse to the various media, the American people were advised to change their diets drastically and especially curtail the consumption of cholesterol to 300 mgs. daily from the usual 600 mgs. and reduce the intake of saturated fats to 35% from 40%. Admittingly having no proof on which to base these revolutionary recommendations that

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TABLE I

ESTIMATED RELATIVE REDUCTION IN CORONARY HEART DISEASE INCIDENCE (v) ASSOCIATED WITH RELATIVE REDUCTION IN SERUM CHOLESTEROL (u)

Relative decrease in serum cholesterol (u)	Relative decrease in coronary heart disease incidence (v)	Relative decrease in serum cholesterol (u)	Relative decrease in coronary heart disease incidence (v)
.06	.160	.31	.617
.11	.294	.36	.695
.16	.371	.41	.754
.21	.466	.46	.836
.26	.535	.50	.882

*Note: Values of v were obtained from relationship $v = 1 - (1 - u)^{4.5}$ as described in Fed. Proc. 21 (Suppl. No. 8) Part 2 June-August, 1962.

The data illustrate the potential importance of the possibility of major declines in CHD mortality in the years to come. For example, a postulated reduction in serum cholesterol of 10% (u = .10) is estimated to yield a 34% decrease in coronary heart disease incidence (v = .34).

affect the life habits of the American people. Either the manufacturing of cholesterol foods and the raising of livestock. The Commission presents some good facts, studies, and tables to support their unproven theories.

On page 455 of the Commission's Report we find Table 16, The Estimated Relative Reduction in Coronary Heart Disease Incidence Associated with Relative Reduction in Serum Cholesterol, referred to as Table I of this article above. The figures (v) were obtained from the relationship $1 - (1 - u)^{4.5}$ as described in a 1962 Com-

socio-economic status, v is the relative incidence of CHD and u is the relative serum cholesterol level. An example is given that a 10% reduction in the serum cholesterol level in the United States population (u = .10) is estimated to yield a 34% decrease in coronary heart disease incidence (v = .34).

Since such great importance is ascribed to this table and since it is utilized in two prior studies[2] we deemed it worthwhile to re-read Cornfield's original work and find out if the statements contained in there correspond with the table published by the Inter-Society Commission. In the entire study of Cornfield, we were unable to find the equation $v = 1 - (1 - u)^{4.5}$ but we do find equation (7), $P = .0091\left(\frac{Y_1}{100}\right)^{2.7}\left(\frac{Y_2 - 75}{100}\right)^{1.6}$ where Y_1 and Y_2 are serum cholesterol and systolic blood pressure respectively.

Cornfield states, "A 1% decrease in cholesterol would be associated with a 2.66% decrease in risk of coronary heart disease throughout the range of cholesterol values." In other words, it is not just limited to the levels of frank hypercholesterolemia, but also applicable to the lower values of cholesterol in the serum without exception. So, it to drive this point home by *reductio ad absurdum*, a lowering of cholesterol level from a normal of 220 mgs to 110 mgs per cent would put a theoretical person at an 81% less risk of coronary heart disease: the same as if lowering the cholesterol from 180 mgs. to 240 mgs per cent, providing that the experimental reduction of cholesterol is of the same risk condition that the Commission fails to mention.

Cornfield states in a personal letter: "My paper, 'Joint Dependence of Risks of Coronary Heart Disease on Serum Cholesterol and Systolic Blood Pressure: a Discriminant Function Analysis' Fed. Proc. 21, Suppl. No. 1, pp 58-61, July-August, 1962 states, 'If one could lower cholesterol levels by a given amount, say 15%, and if equation (7) describes not only the association between risk and cholesterol level in Framingham, but also the change in risk that would accompany an experimental alteration in serum cholesterol, then the relative risk would be .85$^{2.7}$, or a reduction of about 35%.'" Mathematical analysis reveals Cornfield's formula correct insofar as statistical significance is concerned.

Having shown the biological implausibility of the Report's Table 16, we turn to the collection of data for Cornfield's equation. We question this data which was given to him by the Framingham Study and the propriety of numbers from which

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TABLE II[3]

NEW CHD IN 6 YEARS FOLLOW-UP: ACTUAL AND EXPECTED NUMBER OF CASES AMONG MEN 40-59

Serum Cholesterol mg/100 cc.	Systolic B.P. mm Hg.	NEW CHD		Population at Risk
		Expected*	Actual	
200	Total	10.5	12	319
	<117	0.8	2	53
	117-126	1.4		66
	127-136	1.8	2	59
	137-146	2.3	1	65
	147-156	1.6	2	37
	157-166	0.7	1	13
	167-186	1.4	3	21
	187+ over	0.5	1	5
200-209	Total	5.9	2	133
	<117	0.5		21
	117-126	0.8	2	27
	127-136	1.4		34
	137-146	1.0		19
	147-156	1.9		16
	157-166	0.7		10
	167-186	0.4		5
	187+ over	0.1		1
210-219	Total	6.9	6	121
	<117	0.4		15
	117-126	0.9	1	25
	127-136	1.0	2	21
	137-146	1.5		26
	147-156	0.4		6
	157-166	0.9		11
	167-186	1.1		11
	187+ over	0.8	3	6
220-244	Total	22.3	23	334
	<117	0.6		20
	117-126	2.9	8	69
	127-136	4.7	2	83
	137-146	5.5	6	81
	147-156	2.4	3	29
	157-166	1.5	1	15
	167-186	3.1	2	27
	187+ over	1.6	1	10
245-259	Total	11.6	8	136
	<117	0.5		14
	117-126	1.3		24
	127-136	2.3		33
	137-146	2.0	3	23
	147-156	1.9	2	19
	157-166	1.3		11
	167-186	0.7	2	5
	187+ over	1.5	1	7
260-284	Total	16.0	23	156
	<117	1.0	1	22
	117-126	1.4	5	22
	127-136	2.1	2	26
	137-146	3.5	2	34
	147-156	1.9	4	16
	157-166	1.7	2	13
	167-186	2.7	6	15
	187+ over	1.5	1	7
285+ over	Total	18.9	18	130
	<117	0.7		11
	117-126	1.7	1	19
	127-136	3.1	4	28
	137-146	3.1	4	23
	147-156	2.8	1	16
	157-166	2.5	4	12
	167-186	3.2	3	14
	187+ over	1.9	1	7

*Expected number of cases = $\frac{\text{(population at risk)}}{(1 + e^{\text{[illegible]}})}$

Note: Cholesterol determinations were done by the Kendall-Abel method at Framingham, Massachusetts

he derived his equation. We doubt the validity of the application of Cornfield's equation to Table 16 in the Inter-Society Report in view of the latter's simplifications and the omission of the risk of experimental alteration in serum cholesterol levels which Cornfield mentions. According to the Commission's attitude, this risk would be zero. The Commission implies that the reduction mentioned in the footnote to Table 16 would only be valid for the very high levels of serum cholesterol found in hypercholesterolemia, but Cornfield claims his formula is valid for the whole range of cholesterol levels.

A total of 1329 male persons between the ages of 40 to 59 were examined for freedom of coronary heart disease in the Framginham Study. Neither then (1962) nor at the present time can even the most astute diagnostician say with certainty that an individual is free of coronary heart disease. So one of the basic assumptions of the Framingham Study is open to serious doubt.

Of the 1329 allegedly coronary heart disease-free persons only 92 developed various incidents of coronary heart disease, which must have included angina pectoris. Seventy-four were distributed over a range of cholesterol from 200 to 284 mgs per cent, with groupings as high as 23 to a low of 2 persons. The groupings were arbitrarily chosen as shown in Table II reprinted from Cornfield's paper (see at left). A questionable transformation takes place by semantic legerdemain on the part of the Commission. The *risk* of coronary heart disease in 92 persons out of a group of 1329 reported by Cornfield is equated by the Commission to the *incidence* of coronary heart disease in many millions of the U.S., if not the world's, population — a substitution which is unacceptable. Again, we doubt the accuracy of the data presented to the computer.

It is a known fact that cholesterol in the non-fasting individual, as tested in Framingham, is not greatly affected by dietary intake of fats and cholesterol in the short run. From values of our own study, described below, as well as from the world literature we learn that the same individual has variable values of serum cholesterol on different days, different seasons and other circumstances.[3]

Cholesterol was determined in five males and five females of an age group from 18 to 30 on two different occasions. On one occasion a low caloric breakfast was served consisting of two ounces of Ovaltine** dissolved in twelve ounces of milk.

**Ovaltine contains protein (10%), easily emulsified fat (1%) and carbohydrates (75%). Each teaspoonful contains 22 calories.

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TABLE III

SCATTERED VALUES OF SERUM CHOLESTEROL IN A GROUP OF INDIVIDUALS AT VARIOUS TIMES

Key:

○ = Low caloric diet, fasting
□ = High caloric diet, fasting
◉ = Low caloric diet, post-prandial
◘ = High caloric diet, post-prandial

Group A–G is male **Group H–N is female**

Patient→ Serum Level ↓	A	B	C	D	E	F	G	H	I	J	K	L	M	N
150–159										◘				
160–169		◘												
170–179				◉	□					□	□ ◘			
180–189			□		○ □ ◉	□				◉				□
190–199		○ ◉	◘	○				□ ◘		○	○			◘
200–209			◉	◘		◘					◉		□ ◘	
210–219		□	○	□			◘	○ ◉						
220–244	◘						□		C □ ◉			○ □ ◘		
245–259	◉								□			◉		
260–284	○ □													

Note: Accuracy of determinations, by the Libermann-Burchardt method, was ±3.5%.

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...a subsequent day a high caloric breakfast consisting of bacon, eggs, sausages, bread, butter, and orange juice was consumed. Post-prandial blood specimens were examined 15 minutes after the individual finished eating the low caloric meal. Ninety minutes after the high caloric meal post-prandial blood specimens were examined. Four individuals (2 males and 2 females) aged between 30 and 62 consumed the high caloric meal with an addition of 2 ounces of Ovaltine® in 12 ounces of milk. Fasting and 90 minutes post prandial specimens were examined. There was a total of 48 different cholesterol determinations.

It was found that only eight times did the fasting and post prandial specimens pair (see Table III, page 00). The other pairs of fasting and post-prandial values varied significantly in the same individual and projecting this finding to the Framingham Study, 66% of the post-prandial values used in this population group might be subject to grouping changes—a factor that would throw the application of Cornfield's equation to the Framingham Study into serious doubt.

The Framingham blood specimens were taken when convenient to the volunteers regardless of diet, time of the day, or other anamnestic influences. The accuracy of our determinations was ±3.5% as determined by duplicates. If hypercholesterolemia is defined as serum values over 260 mgs per cent, only one individual had such a fasting serum value, and that went down 20-40 mgs per cent post-prandially, jumping two of Cornfield's sample groups. It is also quite presumptuous to project or generalize findings found in a homogeneous northeastern community whose racial and ethnic background is not given and which could have completely different eating habits to embrace the considerable diversity of the United States population. It has been reported by others in epidemiological studies that the death rate from coronary heart disease is different in various states of the Union.[4]

Due to the narrow range chosen by Cornfield in his groupings, an individual's cholesterol level could shift from one of Cornfield's cholesterol groups into another, from day to day, and week to week. This would also apply to blood pressure measurements. These shifts would then raise havoc with Cornfield's formula. Again we find Cornfield's formula palpably wanting biologically though statistically valid, assuming the constancy of starting values.

Cornfield also stresses the fact that the percentage reduction of cholesterol pertains to risk of coronary heart disease in all values of the table high or low. But it is different if one considers the presentation of risk in actual milligram per cent reduction. There we have a large absolute difference in risk when added to a large, rather than to a small, initial level of serum cholesterol.

With complete disregard of the above considerations, the Commission devised its own interpretation of Cornfield's data. Instead of *risk*, we are now told that the coronary heart disease *incidence* is reduced with a relative reduction in serum cholesterol. According to Webster's Dictionary, 2nd edition, risk and incidence have two completely unrelated meanings—

Incidence: act, fact, manner of falling upon or affecting, range of occurrence or influence
Risk: degree of probability of loss or chance of loss

We are now told that a 10% reduction of cholesterol in the population of the United States will yield a decrease of 24.4% in the *incidence* of coronary heart disease. From Table 16 in the Commission's report we can learn that a 50% decrease in serum cholesterol will yield a decrease of 84.2% of the *incidence* of coronary heart disease. Any biologically oriented researcher knows that this is a physiologic impossibility and is absurd in its implication because a 50% reduction of serum cholesterol levels may entail untold dangers.

Cornfield must have sensed these shortcomings because in a later (1969) publication[5] he stated, "We must admit at the outset that we have no secure basis for estimating the reduction in incidence of or mortality from coronary heart disease that could be achieved by application of current knowledge." He also states in the same article, "It seems clear that despite a very considerable scientific effort and some tantalizingly suggestive results, we have no clear-cut generally accepted answer to the question whether cholesterol lowering measures can affect coronary heart disease." We concur in Cornfield's doubts. We feel that his equation is not valid biologically and should not be used to substantiate the implied effect of proposed dietary changes suggested by the Commission.

Obsessed with the idea of correlating values from blood chemistry with actual disease, the Commission was undisturbed by reality and objectivity. Since the Commission's mind was made up in advance, the membership of the Commission did not want to be bothered with the confusing facts. For example, in a study of cigarette smoking, the find-

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ings of Keys and others[2] that there was no connection between cigarette smoking and coronary heart disease in certain European countries was not mentioned, whereas the findings concerning the relationship between cholesterol levels and coronary heart disease in the same study are given prominence. Keys also states in the same study, again not mentioned in the Commission's Report, that the incidence of coronary heart disease is lower among individuals who smoke less than 20 cigarettes per day than among *nonsmokers* or heavy smokers. An unbiased report would not have selected from such omissions.

In a very recent study by Keys[3] we find that in contrast to a value of 2.66 found in the Framingham Study as the exponent for coronary heart disease incidence, a value of 2.21 has now been established. There is also a presentation that angina pectoris was less closely related to serum cholesterol level than it was to myocardial infarction. This result is also duplicated by a study of Western Electric Co employees and Los Angeles civil servants.[4] However, as mentioned before by Gofman[5] in his paper[6] all phases of coronary heart disease are included in the Framingham Study. This again shows the unreliability of his original data.

Furthermore, the statements of Pearce and Dayton,[7] who warn that their findings are not to be construed as recommending reductions in the American diet, are also not discussed in the Commission's Report. Due to their caveat a potential danger from unregulated fats in the commercial market is underplayed. The American people are led to believe that unsaturated fats are beneficial and undergo chemical changes such as hydrogenation during cooking. The truth is that such changes are not well known and may, in fact, be quite harmful. Even the Inter-Society Commission Report[1] states:

> It publication of the individual members concerning the Commission are examined, one finds that in July 1970 [J. L. Dayton] wrote an editorial for the American Journal of Medicine[8] about the prevention of coronary heart disease. The conservative physician must agree that although the data are suggestive, the conclusions are not the fundamental principle that he should do no harm. In December of the same year one finds [another] member of the Commission giving his opinion to other physicians on modifications of dietary changes.

A more cautious view of such dietary changes is reflected in the remarks of Dr. Donald S. Fredrickson, who chaired the Inter-Society Commission Report in his St. Cross Lecture[9] at the National Heart Hospital at the Royal College of Physicians of London, published in the British Medical Journal:[10]

> "Here are some things about the report to be pondered in the light of what is actually known. The unproved emphasis on cholesterol and fats seems heavy-handed. What evidence do we have that an egg a day spells peanuts for all Americans? . . .
>
> ". . . One looks vainly in the Commission Report for something new and strong enough to change the present rational nutritional position concerning dietary fat and cholesterol. . . ."

The Commission disregards the potential economic dislocations which would result from their recommendations, should they become realities. It also completely disregards the warnings and excellent deliberations in the Report of the Ad Hoc Heart Review Panel of the National Heart Institute dated June 1960 and published as American Heart Association Monograph No. 28, 1969, which antedates the Inter-Society Commission Report. The members of that panel have at least the same scientific standing and authority, but act more responsibly than the members of the Inter-Society Commission.

By critical analysis of the Report of the Inter-Society Commission for Heart Disease Resources concerning the prevention of atherosclerosis we are led to endorse the opinions of Ludwig and Co-workers[11] "Errors of presentation include inappropriate generalizations and the inconsistent use of published data." We feel that the Commission presented its findings in a misleading manner.

We quote again from Ludwig and Co-workers[11] "More serious consequences follow when erroneous conclusions are drawn from invalid data or from faulty or incomplete analyses. Health programs may be augmented or discontinued, hypotheses modified and worthless solutions to public problems advanced, all on the basis of misinformation."

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